DEMETHYLATIONS IN THE CULARINE SERIES

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Abstract - Selective demethylation in 7,4',5'-substituted cularine compounds can be achieved under two different sets of conditions (acidic and nucleophilic). Less satisfactory results are obtained in the 7,3',4'-substituted analogs.

INTRODUCTION

The methylation of phenols and the selective O-demethylation of aryl methyl ethers constitutes an important procedure for the interconversion of naturally occurring compounds.[1]

The cularines are a group of isoquinoline alkaloids[2] whose number has recently been increased by the isolation of several new members, mainly of a phenolic nature.[3,4] This fact makes the cularines an interesting choice for demethylation studies. For this purpose we selected two general reagents[5] presenting opposite but in some instances complementary behaviour:

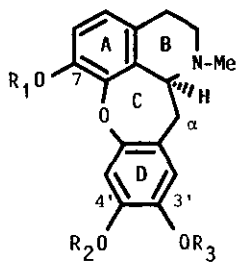
A) 48% HBr/AcOH, an acidic reagent which causes cleavage by a combination of SN1 and/or a partially charged cyclic transition state.

B) EtS^-, a nucleophilic reagent in which the cleavage pattern is essentially SN2.

RESULTS AND DISCUSSION

Demethylation of 3',4'-substituted cularines.- The selective demethylation of cularine 1 under acidic conditions (48% HBr/AcOH, 135°C, 35 min) has been reported[6] as giving 7,3'-didemethylcularine (breoganine) 6. However, in our hands a mixture of demethylated compounds 2-6 was obtained (Table I), breoganine 6 being the major component. By using milder conditions but longer times (65-70°C, 144 h) a mixture of the diphenolics celtisine 5 and breoganine 6 resulted (Table I). These results can be explained assuming that the methoxyl groups at positions 7 and 3' are more basic than that at 4' due to a mesomeric contribution of the oxepinic oxygen.

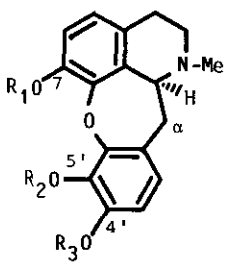
Under nucleophilic conditions[7] the demethylation of cularine 1 occurred preferentially at position 4' (see Table I). When these conditions (NaSEt 5mmol, reflux DMF, 7 h) were used, the monophenolic cularines 3 and 4 produced only the diphenolics celtisine 5 (42%) and breoganine 6 (45%) respectively, together with a certain amount of the initial monophenolic material. The formation of a phenoxide anion in ring D now deactivates the methoxyl group at the ortho-position for a further nucleophilic attack. Treatment of monophenolic cularidine 2 with NaSEt (3mmol, reflux DMF, 2 h) gave the expected diphenols 5 (43%) and 6 (26%) in similar proportions as in the case of cularine 1.



Reaction conditions / Product	48% HBr/AcOH(1:1) 135°C 35 min	48% HBr/AcOH(1:1) 65-70°C 144 h	NaSEt(3mmol) DMF/reflux 40 min	NaSEt(5mmol) DMF/reflux 4 h
cularidine 2 (R_1=H,R_2=R_3=Me)	3	--	15	--
celtine 3 (R_1=R_3=Me,R_2=H)	3	--	33	--
3'-O-demethyl-cularine 4 (R_1=R_2=Me,R_3=H)	10.5	--	21	--
celtisine 5 (R_1=R_2=H,R_3=Me)	18	21	13	43
breoganine 6 (R_1=R_3=H,R_2=Me)	30.5	36	10	18

Table I.- Yields in % for demethylation products of cularine 1 (R_1=R_2=R_3=Me) under different conditions. All products have been identified by comparison with authentic samples.[3] Separation of cularidine 2 and celtine 3 was accomplished by their transformation into their O-acetyl derivatives (see experimental).

Demethylation of 4',5'-substituted cularines.- The demethylation of sarcocapnine 7 under various conditions indicated in Table II ocurred preferentially at its more hindered methoxyl group, that at 5' position. Under milder acidic conditions (60°C) demethylation at 5' was mainly observed, but a higher temperature (90°C) resulted in catechol 10, which has not been found in nature. Its identity was confirmed by conversion into the methylenedioxy derivative 12 (R_1=Me, R_2+R_3=-CH_2-) through methylenation with CH_2Br_2.[8] However, a change in demethylation selectivity was observed when sarcocapnine 7 was treated with NaSEt, which gave claviculine 9. The initial loss of the methyl group at 5' position now ensures that the second demethylation takes place at 7 position.



Reaction conditions / Product	48% HBr/AcOH(1:2) 60°C 14 h	48% HBr/AcOH(1:2) 60°C 30 h	48% HBr/AcOH(1:2) 90°C 60 h	NaSEt(3mmol) DMF/reflux 1 h	NaSEt(5mmol) DMF/reflux 2 h
sarcocapnine 7 (R_1=R_2=R_3=Me)	31	--	--	28	--
sarcocapnidine 8 (R_1=R_3=Me,R_2=H)	56	58	--	6	--
claviculine 9 (R_1=R_2=H,R_3=Me)	--	--	--	22	77
10 (R_1=Me,R_2=R_3=H)	--	10	47	--	--
11 (R_1=R_2=R_3=H)	--	--	8.5	--	--

Table II.- Yields in % for demethylation products of sarcocapnine 7 (R_1=R_2=R_3=Me) under different conditions. All known products have been identified by direct comparison with authentic samples.[3]

EXPERIMENTAL

All melting points were measured in a Büchi apparatus and are uncorrected. NMR spectra were determined with a Bruker WM-250 spectrometer using TMS as internal reference. Mass spectra were run on a KRATOS MS-25 instrument operating at 70 eV. Microanalysis for C, H, N, were carried out on a Perkin-Elmer 240-B elemental analyzer.
1 mm and 0.2 mm layers of Merck 60 GF_{254} silica gel were normally used for preparative and analytical thin layer chromatography, respectively; the solvent systems were benzene-ethyl acetate-diethyl amine (7:2:1) for initial separation of phenolic compounds and methylene chloride-ethyl alcohol (9.5:0.5) for further purification and for separation of non-phenolic compounds.
48% HBr was redistilled over a trace of 50% hypophosphorous acid. 80% NaH in oil dispersion was supplied by Merck.

General procedure

A) Demethylation in acidic conditions.- 0.58 mmol of substrate were dissolved in 3 ml of 48% HBr-AcOH (1:1 or 1:2) and heated under an inert atmosphere during the time indicated. The reaction mixture was diluted with water (10 ml), neutralized with $NaHCO_3$ and extracted with CH_2Cl_2 (5x15 ml). The extracts were dried and evaporated to give a residue which was subjected to preparative thin layer chromatography.

B) Demethylation using a nucleophilic reagent.- Ethanethiol (2.1 mmol) dissolved in dry DMF (1 ml) was added dropwise to a suspension of sodium hydride (2.1 mmol) in dry DMF (2 ml) under an atmosphere of nitrogen. The mixture was stirred for 5 min before addition of a solution of the cularine compound (0.70 mmol) in dry DMF (2 ml) and then refluxed during the time indicated in the table, evaporated, water added, and extracted with CH_2Cl_2 (5x20 ml). The extracts were dried and evaporated to give a solid residue which was purified as above.

Separation of cularidine 2 and celtine 3.- The fraction containing cularidine 2 and celtine 3 was dissolved in dry pyridine (1 ml), 0.5 ml of acetic anhydride added and the solution refluxed during 1 h. Then the mixture was evaporated, water added and after extraction with CH_2Cl_2 afforded a mixture of acetates which was subjected to preparative tlc.

O-Acetylcularidine.- Crystallized from ethanol-ether as its hydrochloride mp 250-252°C (dec.). PMR ($CDCl_3$, 250MHz, δ): 2.39(s, 3H, $OCOCH_3$), 2.57(s, 3H, NMe), 2.70-3.30(m, 6H, 3x-CH_2), 3.79(s, 3H, OMe), 3.84(s, 3H, OMe), 4.35(dd, J_{AX}=11.7 Hz, J_{BX}=3.5 Hz, 1H, H-1), 6.50(s, 1H, Ar-H), 6.56(s, 1H, Ar-H), 6.88(d, J=8.3 Hz, 1H, Ar-H), 6.92(d, J=8.3 Hz, 1H, Ar-H). MS m/e(%): 369(M^+, 57), 354(100), 312(91), 69(82). Anal. Calcd for $C_{21}H_{23}NO_5$(free base): C, 68.29; H, 6.23; N, 3.79. Found: C, 68.01; H, 6.29; N, 4.07.

O-Acetylceltine.- Cristallized from ethanol mp 175-177°C. PMR($CDCl_3$, 250 MHz, δ): 2.29(s, 3H, $OCOCH_3$), 2.57(s, 3H, NMe), 2.72-3.33(m, 6H, 3x-CH_2-), 3.74(s, 3H, OMe), 3.81(s, 3H, OMe), 4.44(dd, J_{AX}=12 Hz, J_{BX}=3.7 Hz, 1H, H-1), 6.60(s, 1H,

Ar-H), 6.74(d, J=8.4 Hz, 1H, H-6), 6.86(d, J=8.4 Hz, 1H, H-5), 7.00(s, 1H, Ar-H). MS m/e(%): 369(M^+, 68), 354(44), 326(17), 312(100). Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.29; H, 6.23; N, 3.79. Found: C, 68.33; H, 6.34; N, 3.45.

Hydrolysis of O-acetyl compounds.- To a solution of 0.05 g (0.135 mmol) of O-acetyl compound in methanol (5 ml) was added in one portion 0.1 g of anhydrous Na_2CO_3. The mixture was stirred at room temperature during 1 h, diluted with water (25 ml), saturated with NH_4Cl and extracted with CH_2Cl_2 (3x15 ml) to afford the corresponding phenolic compound.

Diphenol 10.- Cristallized from ethanol-ether as its hydrochloride mp 248-250°C (dec.). PMR($CDCl_3$), 250 MHz, δ): 2.59(s, 3H, NMe), 2.84-3.47(m, 6H, 3x-CH_2-), 3.87(s, 3H, OMe), 4.53(dd, J_{AX}=12.3 Hz, J_{BX}=4.2 Hz, 1H, H-1), 6.47, 6.59, 6.76 and 6.91(4d, J=8.4 Hz, 1H each, 4xAr-H). MS m/e(%): 313(M^+, 100), 298(27), 296(40) 282(27), 175(19), 174(31). Anal. Calcd for $C_{18}H_{20}NO_4Cl$: C, 61.80; H, 5.72; N, 4.00. Found: C, 61.30; H, 5.96; N, 3.63.

Triphenol 11.- Highly hygroscopic material. Cristallized as its hydrochloride mp 206-208°C. PMR($CDCl_3$+CD_3OD, 250 MHz, δ): 2.58(s, 3H, NMe), 2.60-3.38(m, 6H, 3x-CH_2-), 4.48(dd, J_{AX}=12.2 Hz, J_{BX}=4.0 Hz, 1H, H-1), 6.44(d, J=8.5 Hz, 1H, Ar-H), 6.56(d, J=8.5 Hz, 1H, Ar-H), 6.74(d, J=8.3 Hz, 1H, Ar-H), 6.80(d, J=8.3 Hz, 1H, Ar-H). MS m/e(%): 299(M^+, 100), 272(82), 256(11), 255(11), 132(32). Anal. Calcd for $C_{17}H_{18}NO_4Cl.H_2O$: C, 57.70; H, 5.65; N, 3.96. Found: C, 57.38; H, 5.54; N, 3.70.

Methylenation of catechol 10.- Anhydrous KF (0.082 g, 1.58 mmol) was added to a solution of catechol 10 (0.1 g, 0.32 mmol) in anhydrous DMF (2 ml). Then dibromomethane (0.061 g, 0.352 mmol, 10% excess) was added to the solution and the mixture heated at 110°C under an argon atmosphere for 2 h. Evaporation to dryness followed by addition of water (15 ml), extraction with CH_2Cl_2 (5x15 ml), drying and evaporation afforded a residue which was separated by tlc to give 0.030 g of 10 and 0.035 g of 12.

Compound 12 crystallized from ethanol-ether as its hydrochloride mp 172-174°C (dec.). PMR($CDCl_3$, 250 MHz, δ): 2.62(s, 3H, NMe), 2.80-3.38(m, 6H, 3x-CH_2-), 3.88(s, 3H, OMe), 4.42(dd, J_{AX}=11.8 Hz, J_{BX}=3.0 Hz, 1H, H-1), 5.98(d, J=1.4 Hz, 1H, OCH_2O), 6.09(d, J=1.4 Hz, 1H, OCH_2O), 6.52(d, J=8.1 Hz, 1H, Ar-H), 6.56(d, J=8.1 Hz, 1H, Ar-H), 6.80(d, J=8.4 Hz, 1H, Ar-H), 6.91(d, J=8.4 Hz, 1H, Ar-H). MS m/e(%): 325(M^+, 100), 310(31), 308(52), 294(27), 174(50). Anal. Calcd for $C_{19}H_{20}NO_4Cl$: C, 63.07; H, 5.53; N, 3.87. Found: C, 62.81; H, 5.42; N, 4.21.

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